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# Renal Failure in Wilms' Tumor Patients: A Report From the National Wilms' Tumor Study Group

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This report defines the incidence and determines the etiology of renal failure (RF) in patients undergoing treatment for Wilms' tumor (WT). The database of the National Wilms' Tumor Study (NWTS) was searched to identify all children reported to have developed chronic renal failure. There were 55 patients found to have RF. Of these, 39 patients had bilateral tumors, 15 with unilateral disease and one with a WT in a solitary kidney. The median interval from diagnosis to the onset of renal failure was 21 months. The incidence of RF in bilateral WT was 16.4% for NWTS-1 & -2, 9.9% for NWTS-3, and 3.8% for NWTS-4. The incidence of RF in unilateral WT remained stable. The most common etiologies of RF were: bilateral nephrectomy for persistent or recurrent tumor (24 pts), Drash syndrome (12 pts), progressive tumor in the remaining kidney (5 pts), radiation nephritis (6 pts), and other causes (5 pts). The etiology of renal failure was not reported in three children. Children with unilateral WT and a normal contralateral kidney have a very low incidence of RF, and this review does not support a recommendation for parenchymal sparing procedures in these patients. Children with bilateral WT are at risk for the development of RF, and parenchymal sparing procedures are warranted.


**Key words:** Wilms' tumor, renal failure, late effects

## INTRODUCTION

As the treatment of childhood cancer has improved over the years, clinicians have been faced with the task of treating the late effects of anticancer therapy. Children with Wilms' tumor are at greater risk for impaired renal function from radiation therapy to the remaining nephrons [1], use of potentially nephrotoxic chemotherapeutic agents, and a theoretical risk due to hyperfiltration of the remaining nephrons following removal of a critical mass of renal tissue [2]. Parenchymal sparing procedures have been advocated for children with bilateral Wilms' tumor to preserve as much functioning renal tissue as possible [3–6]. Patients initially receive chemotherapy to shrink the tumor and facilitate renal parenchymal sparing procedures. Recently, other authors have advocated this approach for patients with unilateral Wilms' tumors [7,8]. This review examines the risk of developing renal failure in children who have been registered to the National Wilms' Tumor Study (NWTS).

## MATERIALS AND METHODS

From October 1969 until July 1993, 5,823 children were registered to the NWTS in the randomized or followed categories. Followed patients include those who were not randomized for various reasons but were treated according to one of the NWTS treatment regimens. There were 451 children with bilateral Wilms' tumor and four patients with Wilms' tumor involving a solitary kidney. The remainder had unilateral tumors. All records sent to the Data and Statistical Center are abstracted for information on medical conditions that could represent the development of renal disease. These include hypertension, proteinuria, renal insufficiency/failure, hemodialysis, peritoneal dialysis, or renal transplantation. The charts of all patients with any of these late sequelae reported were reviewed in detail.

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**TABLE I. Incidence of Renal Failure for Patients With Wilms' Tumors**

| | Bilateral synchronous #pts/total (%) | Bilateral metachronous #pts/total (%) | Unilateral Wilms' #pts/total (%) | Mononephric #pts/total (%) | Total #pts/total (%) |
|---|---|---|---|---|---|
| NWTS-1 | 3/29 (10.3) | 4/12 (33.3) | 2/515 (0.38) | 0/0 (0) | 9/556 (1.6) |
| NWTS-2 | 5/36 (13.8) | 2/8 (25.0) | 3/735 (0.41) | 0/0 (0) | 10/779 (1.3) |
| NWTS-3 | 15/158 (9.5) | 3/23 (13.0) | 4/1,977 (0.20) | 1/2(50) | 23/2,160 (1.1) |
| NWTS-4 | 7/168 (4.2) | 0/17 (0) | 6/2,141 (0.28) | 0/2 (0) | 13/2,328 (0.6) |

**TABLE II. Incidence of Renal Failure Correlated With the Duration of Follow-Up***

| | No. pts | No. pts with renal failure | Incidence of renal failure (%) @ 2 yr | 4 yr | 8 yr | 16 yr |
|---|---|---|---|---|---|---|
| Unilaterals | 5312 | 15 | 0.1 | 0.2 | 0.3 | 0.6 |
| Bilaterals | | | | | | |
| NWTS-1 | 41 | 7 | 9.8 | 9.8 | 9.8 | 16.6 |
| NWTS-2 | 43 | 7 | 14.6 | 14.6 | 14.6 | 22.3 |
| NWTS-3 | 181 | 18 | 6.6 | 8.3 | 11.6 | 12.7 |
| NWTS-4 | 177 | 7 | 2.6 | 5.8 | 5.8 | — |

*Nine bilateral patients excluded from this analysis due to short follow-up. Fifty-six unilateral patients excluded due to lost to follow-up. Difference in the incidence of renal failure in patients with unilateral and bilateral patients is statistically significant, $P < 0.0001$.

All children who were identified to be on long-term dialysis or who have undergone renal transplantation are included in this report. For those patients that remain on medical management, RF was defined as a serum creatinine > 2.5 mg/dl. Patients with transient elevations in serum creatinine during treatment that resolved are not included in this report.

The records of all patients entered into the Late Effects Study were also reviewed for adverse events. All randomized and followed patients who have survived 5 years from diagnosis are eligible for the Late Effects Study of the NWTS [19]. Two forms are submitted for these patients, a medical history form and a physical examination form. The latter includes the patients serum creatinine as well as physical findings. As of April 1, 1993, 3,481 patients were eligible for the Late Effects Study. The number of eligible patients who have been followed alive 10, 15, and 20 years after diagnosis are 2,063, 887, and 275, respectively.

If complete data on the etiology and/or management of the renal failure (dialysis, transplantation) had not been reported to the DSC, the individual institution or treating physician was contacted.

## RESULTS

A total of 55 patients with renal failure were identified. The reporting of these patients for each of the NWTS trials is shown in Table I. There has been a trend for a decreasing incidence of RF in bilateral WT with calendar period, but this difference was not significant, $P = 0.2$ (Table II). The incidence of RF in unilateral WT remained stable (Fig. 1). The interval from diagnosis to the onset of renal failure ranged from 0 days to 21 years (median of 21 months). Median follow-up was 6 years from diagnosis (range 2 months to 22 years). Thirty-nine of the patients with renal failure had bilateral Wilms' tumor, synchronous or metachronous. In this group, the most common etiology for the renal failure was bilateral nephrectomy for persistent or recurrent tumor (Table III), which was performed in 24/39 (62%) patients with bilateral tumors. In 17 of these children, the initial management included an unilateral nephrectomy prior to the initiation of chemotherapy. The second nephrectomy was performed at a median interval of 21 months (range 0–79 months) from diagnosis for synchronous tumors and at a median of 56 months (range 41–63 months) from initial nephrectomy for metachronous tumors. All the metachronous bilateral tumors were >6 cm in diameter at diagnosis. Of the synchronous bilateral tumors, 43 tumors were >6 cm in diameter, four were 3–6 cm in diameter, and 11 were <3 cm in diameter at diagnosis. Tumor size was not available for one child. This suggests that even children with small tumors in one kidney at diagnosis are at risk for subsequent renal loss/damage.

Five patients developed renal failure due to progressive tumor in the remaining kidney. All of these patients died with a median of 9 months from diagnosis to death. None of these patients underwent total nephrectomy. The incidence of renal failure was greater among patients with metachronous bilateral Wilms' tumor, but the rate of renal failure in patients with metachronous tumors has decreased considerably during the past 25 years (Table I).

For patients with unilateral Wilms' tumor, the Denys-

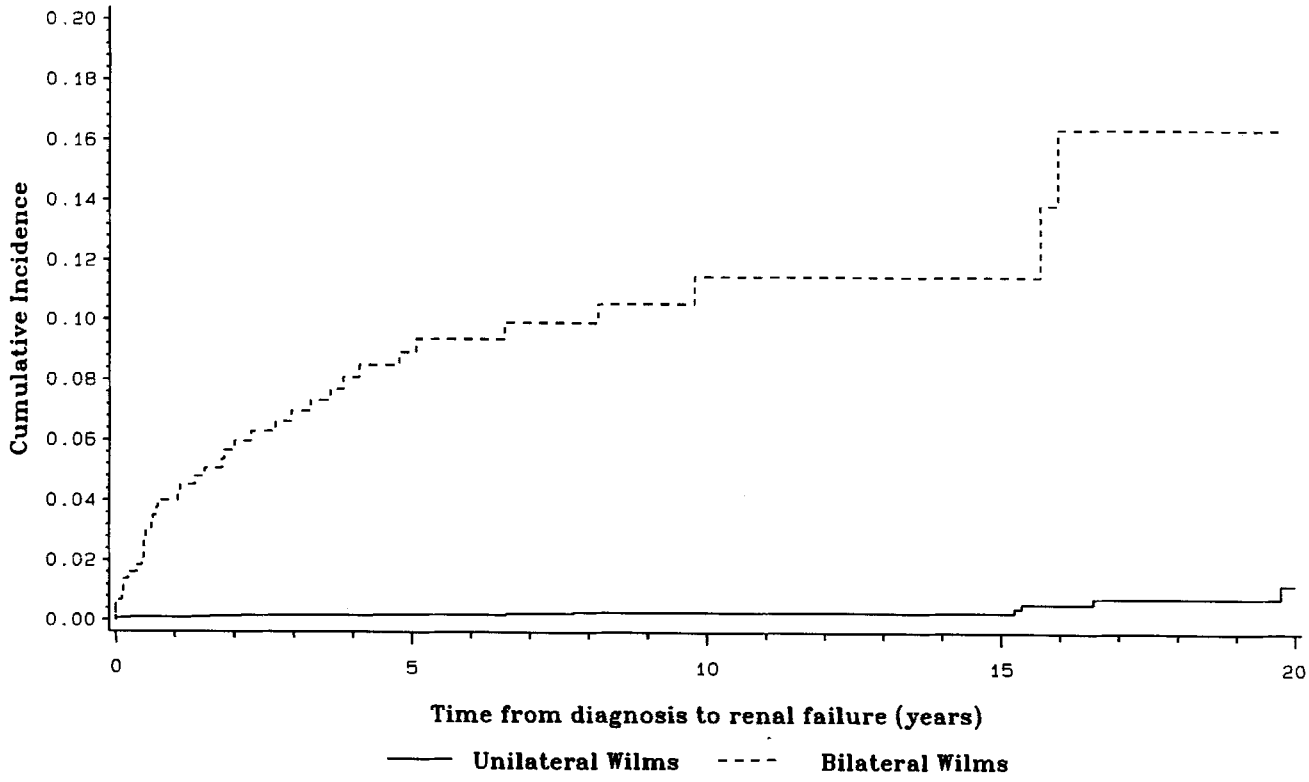


**Fig. 1.** NWTS cumulative incidence of renal failure.

**TABLE III. Etiology of Renal Failure**

| | No. pts. |
|---|---|
| Unilateral Wilms' tumor (15 patients) | |
| Denys-Drash syndrome | 10 |
| Radiation nephritis | 3 |
| Rapidly progressive glomerulonephritis | 1 |
| Unknown | 1 |
| Solitary kidney (1 patient) | |
| Nephrectomy for tumor | 1 |
| Synchronous bilateral Wilms' tumor (30 patients) | |
| Bilateral nephrectomy for tumor | 17 |
| Extensive tumor involvement | 3 |
| Radiation nephritis | 3 |
| Denys-Drash syndrome | 2 |
| Surgical complications | 1 |
| Renal artery stenosis | 1 |
| Hydronephrosis | 1 |
| Unknown | 2 |
| Metachronous bilateral Wilms' tumor (9 patients) | |
| Bilateral nephrectomy for tumor | 7 |
| Extensive tumor involvement | 2 |

Drash syndrome was the most common cause of renal failure [10,11], followed by radiation nephritis. The latter was confirmed by biopsy in one patient. In two children, a clinical diagnosis of radiation nephritis was based on the onset of hypertension, proteinuria, and progressive renal failure. The radiation dose to the remaining kidney in these three patients was 1,500, 1,800, and 2,000 cGy, respectively.

## Treatment of Renal Failure

Twenty-five patients have undergone renal transplantation; 11 of these were living related and 14 cadaveric transplants. Renal transplantation was performed at a median interval of 4.5 years from diagnosis, (range 7 months to 20 years). There were no patients with tumor relapse or tumor-related death after transplantation. Twenty-one children were on dialysis at last follow-up.

The renal failure was medically managed in nine patients, (six at the time of death and three at last follow-up). The serum creatinine exceeded 3.5 mg/dl in eight of these patients. The other child died from complications of hypertension and congestive heart failure.

## Radiation Therapy

Twenty-four of the 55 patients received radiation therapy to the renal parenchyma. Nine of these patients subsequently underwent bilateral nephrectomy. In the other 15 children, the radiation dose to the remaining renal parenchyma ranged from 1,180 to 2,000 cGy. Six of

these patients developed radiation nephritis, three children with unilateral tumors and three with bilateral tumors.

### Survival

Twenty-two patients have died. Sixteen deaths were due to tumor progression. Five deaths were related to complications of dialysis or renal failure. This was due to sepsis in one patient, hypertension with intracerebral hemorrhage in another, and hypertension and congestive heart failure in three. One child died from infectious complications after a renal transplant.

## DISCUSSION

The risk of developing renal insufficiency after unilateral nephrectomy is largely unknown. Studies in adults have found that the late occurrence of renal dysfunction after nephrectomy is uncommon [12]. However, there is both clinical and experimental evidence that the reduction of the total number of nephrons, such as following unilateral nephrectomy, can lead to renal dysfunction secondary to chronic hyperfiltration of the remnant nephrons [2]. Most experimental studies involve a loss of >3/4 of the total renal mass. The data in humans regarding renal damage from hyperfiltration following nephrectomy is less clear. The renal lesion that occurs in animals that progress to renal failure following subtotal renal ablation is focal glomerulosclerosis. This lesion has been found in patients who have >50% of their renal mass removed. Novick et al. [13] reported that 9 of 14 adult patients developed proteinuria after such treatment for renal cell carcinoma. Biopsies revealed focal glomerulosclerosis in four patients, two of whom developed renal failure. The extent of proteinuria was inversely correlated with the amount of remaining renal tissue and directly with the duration of follow-up. There have been only three children reported to have developed focal segmental glomerulosclerosis many years after completion of treatment for Wilms' tumor [14,15]. The only patient to develop renal failure also had renal artery stenosis of the solitary kidney and had received abdominal irradiation [15].

These data suggest that humans are at increased risk for late renal dysfunction if a critical mass of renal tissue is removed. Children with bilateral Wilms' tumor frequently require removal of >50% of their renal tissue and therefore fall into this high risk group. Synchronous bilateral Wilms' tumor accounts for 5% of all patients registered to the NWTS [5]. Prior to the initiation of the NWTS ablative surgery was considered to be essential for cure, since these patients were thought to have a poor survival. For some patients with synchronous bilateral tumors this resulted in significant renal insufficiency or an anephric patient requiring renal transplantation [16–18]. In 1977, Bishop et al. [3] reviewed the early experience of the NWTS with bilateral tumors and found that survival was comparable to other Wilms' tumor patients. Later reports from the NWTS [4] and others [6] have shown that there is no difference in survival for patients managed initially with chemotherapy after biopsy versus those undergoing primary surgical resection. The use of cytoreductive chemotherapy prior to surgical resection is now recommended for all children with synchronous bilateral tumors to allow greater renal preservation and avoid renal insufficiency [19].

This study demonstrated that the most common cause of renal failure in children with bilateral Wilms' tumor is persistent or recurrent tumor in the remaining kidney after initial nephrectomy. This was the cause of renal failure in 74% of the patients with bilateral tumors reported to the NWTS. Treatment related injury (radiation-induced damage, surgical complications) of the remaining kidney was the second leading cause of renal insufficiency. We did not find evidence that many children developed renal insufficiency secondary to focal glomerulosclerosis. Only two patients with bilateral tumors had no cause reported for the renal failure. Even if these patients are assumed to have renal failure secondary to hyperfiltration injury, the incidence is far less than that reported by Novick et al. [12] despite the fact that the median follow-up for NWTS -1, -2, & -3 bilateral patients of 8.0 years is comparable to the 7.7 years reported in the Cleveland clinic series.

There are only limited data assessing long-term renal function in children following unilateral nephrectomy. Whereas several studies have found no significant alterations in renal function following unilateral nephrectomy for Wilms' tumor [20–23], other reports have noted an increased incidence of proteinuria and decreased GFR. One study of 27 patients (4 had Wilms' tumor) evaluated a mean of 23.3 years after nephrectomy found only minimal changes in GFR when compared to controls and none had significant proteinuria or hypertension [24]. Another report of 27 patients with Wilms' tumor noted that 33% had a creatinine clearance <55 ml/min/1.73 $m^2$, but did not state whether any of these patients had proteinuria or other clinical manifestations of renal insufficiency [25]. Argueso et al. [26] reported that 30% of children with acquired solitary kidneys followed a mean of 25 years after nephrectomy were at increased risk of proteinuria and renal insufficiency, although none had developed end-stage renal disease.

Levitt et al. [27] evaluated 53 patients at a mean of 13 years after treatment for Wilms' tumor. Ten patients (19%) were found to have a decreased GFR (<80 ml/min/1.73 $m^2$), six patients (11%) had hypertension, and five (9%) had increased urinary excretion of albumin. None of the patients had developed renal failure. Forty of the 53 patients had received radiation (300–1,720 cGy) to the remaining kidney. Factors found to be associated with

renal dysfunction were age <24 months, and radiation doses >1,200 cGy to the remaining kidney. All six patients with radiation nephritis as the etiology for the renal failure in this review received radiation doses exceeding 1,200 cGy to the remaining kidney. The correlation of functional impairment with the renal radiation dose was reported by Mitus and others in a review of 100 children treated for Wilms' tumor [1]. The incidence of impaired creatinine clearance was significantly greater for children receiving >1,200 cGy to the remaining kidney and all cases of overt renal failure occurred in patients who had received >2,300 cGy.

Although the incidence of clinically relevant problems is low, the concern of renal dysfunction has led some surgeons to recommend parenchymal sparing procedures for unilateral tumors [7]. Most Wilms' tumors are too large for a partial nephrectomy at initial presentation. One study noted that only 5% of nonmetastatic unilateral Wilms' tumors were amenable to a partial resection at presentation [28]. Resectability was based on the presence of a functioning kidney, no invasion of the collecting system or renal vein, clear margins between the tumor, kidney, and surrounding structures, and tumor involving only one pole occupying < one-third of the kidney. After preoperative chemotherapy, 10–20% of patients may then be amenable to partial nephrectomy. McLorie et al. [7] found that 4 of 30 children with unilateral disease were amenable to partial nephrectomy after 4–6 weeks of vincristine and dactinomycin. Another recent report noted that seven of 79 patients with unilateral Wilms' tumor were able to undergo partial nephrectomy after pretreatment according to the SIOP protocol [8]. None of the patients developed local recurrence at a median follow-up of 65 months. The largest experience with the use of preoperative chemotherapy to facilitate partial nephrectomy is in patients with bilateral tumors [3–6]. Montgomery et al. [5] found that partial nephrectomy was feasible in >30% of patients with bilateral tumors treated with initial chemotherapy.

Disadvantages of such an approach for unilateral tumors include the potential for increased surgical complications and the possibility of local recurrence. If we could accurately predict which patients with unilateral disease are at risk for subsequent contralateral tumors, this approach would be easier to justify on an individual basis. If nephrogenic rests are found in the adjacent renal parenchyma, there is an increased risk of metachronous tumors [29]. Unfortunately, at the present time these patients are generally identified after nephrectomy is completed. The exception is the patient found to have nephrogenic rests on exploration of the contralateral kidney. If a biologic marker could be identified that correlated with the presence of nephrogenic rests, patients could be selected for a parenchymal sparing approach. Until then, partial nephrectomy should be reserved for only a select group of patients.

## CONCLUSIONS

We conclude that parenchymal sparing operations should be considered in the following situations: the rare patient with renal insufficiency at presentation, a Wilms' tumor in a solitary kidney, or bilateral Wilms' tumors. The data show an increased risk of renal failure in these selected patients, some of whom will eventually have >50% of their total renal mass removed. The use of initial preoperative chemotherapy, rather than radical surgery, will facilitate the use of parenchymal sparing operations with the potential advantage of decreasing the incidence of end-stage renal disease in this high-risk group of patients. For other patients with unilateral Wilms' tumors and a normal contralateral kidney, the risk of renal failure is far lower, and this review does not support a recommendation for parenchymal sparing procedures in these patients. However, the development of renal insufficiency in all children with Wilms' tumor remains a concern. Although we found a low incidence, 0.25%, of renal failure in children with unilateral Wilms' tumor, many of these children have yet to reach adulthood and could experience subtle renal deterioration at long-term follow-up. It is important that these children have long-term follow-up with measurements of blood pressure, urine protein, and serum creatinine. This will allow a better assessment of the actual risk of renal failure in children cured of Wilms' tumor.

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